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(19)

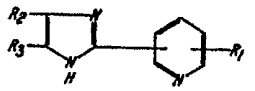
(72) Inventor JOHN J. BALDWIN

(54) IMIDAZOLE DERIVATIVES

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

It is known that certain imidazole compounds are useful as xanthine oxidase inhibitors or as anti-hypertensive agents, and that xanthine oxidase inhibitors are useful in the treatment of gout. (See British Patent No. 1,301,754). The present invention is concerned with other substituted imidazole compounds, which are also useful as xanthine oxidase inhibitors or in the treatment of hypertension and thus serve as alternative compounds for those already known.

The compounds of the present invention have the general formula:



where R_1 is hydrogen or C_{1-3} alkyl, R_2 is halogen and R_3 is halogen or trifluoromethyl; or are pharmaceutially acceptable salts thereof. Preferably, R_1 is hydrogen, R_2 is chlorine or bromine and R_3 is chlorine, bromine or trifluoromethyl.

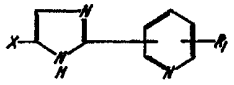
Also in accordance with the present invention, there is provided a method of inhibiting xanthine oxidase or lowering blood pressure in a non-human animal, that comprises administering to the animal a therapeutically effective amount of a compound of the invention.

The compounds of the present invention are generally administered in amounts of from 0.005 to 300 mg/kg, preferably from 0.05 to 100 mg/kg and particularly from 0.1 to 25 mg/kg, of body weight of the animal. The dosage must be adjusted depending upon the activity of the compound, the response desired in the animal and also the weight of the animal. In the ranges given above, the more active compounds would tend to be given at the lower dosages and the less active compounds at the higher dosages.

The present invention further provides a pharmaceutical composition comprising an inert pharmaceutically acceptable diluent and, as active ingredient, a compound of the invention.

In a single dosage form of such a composition of the present invention, the active ingredient is generally present in the composition in amounts of from 1 mg to 2 g, preferably 5 mg to 1 g and particularly 10 to 500 mg. The compound may be administered in a single slow-acting dose or it may be administered in several small doses throughout the day, generally 2 to 8 individual doses.

The present invention also provides a process for preparing the novel compounds by reacting a compound of the formula:



where R_1 is as defined above and X is hydrogen or trifluoromethyl, or a pharmaceutically acceptable salt thereof with a halogenating agent in an inert solvent.

The reaction is preferably carried out at a temperature of from −100°C to 200°C, particularly −15°C to 150°C. In practice, a temperature from 0°C to 125°C, which it is easy to accomplish on both a laboratory scale and a commercial scale by the use of ice water or a simple heating system, is normally used.

The expression "pharmaceutically acceptable salt" is used to mean the non-toxic pharmaceutically acceptable quaternary ammonium and inorganic acid salts such as the methiodide, ethiodide, hydrochloride and hydrobromide salt.

The term "halogenating agent" is used in its broad sense to mean any chemical compound that will supply a halogen atom in a reaction. Preferably the halogenating agent is a "positive halogen" compound or a "positive halogen" donor which supplies bromine, iodine or chlorine in a positive valency state. The various materials which will supply "positive halogen" are well known in the art [see Fresenius 'Angewandte Chemie' (1952) pages 470—478 and Arotsky et al 'Quarterly Reviews' Volume 16 (1962) pages 282—297] and include the hypohalous acids and the alkali metal and alkaline-earth metal hypochlorites such as sodium hypochlorite, potassium hypochlorite, calcium hypochlorite. Free halogens such as Cl_2, Br_2, and I_2 will also furnish positive halogen as does chloramine. Other sources of "positive halogen" are the N-haloamides such as N-chloroacetamide, N-chlorosuccinimide, N-chlorocaprolactam, N-chlorourea and N-chlorohydantoin, as well as the N-bromo and N-iodo analogues of these compounds. All of these materials are well known. However, when using sources of "positive halogen" that are unstable in aqueous systems such as pyridinium perbromide and the alkyl hypochlorites such as *t*-butyl hypochlorite, inert organic solvents such as dioxane, hexane, chloroform, carbon tetrachloride and alkanols are utilized. The expression "inert solvent" merely signifies a liquid in which the reaction can be carried out without the liquid interfering with the reaction.

The compounds of the present invention can be used in the form of compositions preferably administered in unit dosage form such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions or oral administrable solutions or suspensions. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and fractionally similar materials as pharmaceutical diluents or carriers. The tablets or pills of the novel compositions can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol and cellulose acetate. A particularly advantageous enteric coating comprises a styrene maleic acid copolymer together with known materials contributing to the enteric properties of the coating. The compounds are also useful when administered in the form of suppositories or with a penetrant such as dimethyl sulfoxide.

The liquid forms in which the novel composition of the present invention may be incorporated for administration include suitably flavored emulsions with edible oils, such as cottonseed oil, sesame oil, coconut oil and peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, and gelatin. Sterile suspensions or solutions are required for parenteral use. Isotonic preparations containing suitable preservatives are also highly desirable for injection use.

The term single dosage form as used in the specification refers to physically discrete units suitable as unitary dosage for warm-blooded animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel single dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active materials and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in warm-blooded animals as disclosed in detail in this specification. Examples of suitable oral single dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, teaspoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

The following examples are given to illustrate the invention and are not intended to limit it in any manner. All parts are given in parts by weight uless otherwise expressed.

EXAMPLE 1

2-(3-Pyridyl)-4,5-dichloroimidazole

To a suspension of 2 - (3 - pyridyl) - imidazole (1.5 g., 0.01 mole) in chloroform (150 ml.) is added dropwise with stirring over one hour at reflux N-chlorosuccinimide (2.6 g., 0.02 mole). The reaction mixture is heated three hours at reflux. After cooling, the solvent is removed at 20 mm. and the residue triturated with water while heating on a steam bath. The resulting solid is filtered and after recrystallization from acetonitrile 400 mg. of

2 - (3 - pyridyl) - 4,5 - dichloroimidazole is obtained, m.p. 237—238°C.

Anal. calcd.: N, 19.63; C, 44.86; H, 2.35
Found: N, 19.68; C, 45.11; H, 2.38

EXAMPLE 2

2-(4-Pyridyl)-4(5)-bromo-5(4)-trifluoromethylimidazole

To a suspension of 2 - (4 - pyridyl) - 4-trifluoromethylimidazole (2.1 g., 0.01 moles) in chloroform (100 ml.) is added dropwise with stirring at room temperature bromine (1.6 g., 0.01 moles) in chloroform (5 ml.). The resulting solution is stirred for four hours at room temperature and concentrated at 20 mm. pressure over steam to a solid. Water (25 ml.) is added to the residue. The resulting solution is neutralized with saturated aqueous sodium bicarbonate solution, sodium bisulfite (0.5 g.) is added and the precipitated solid is filtered. After recrystallization from acetonitrile, 1.25 g. of 2 - (4 - pyridyl) - 4(5)-bromo-5(4) - trifluoromethylimidazole is obtained, m.p. 216—217°C.

Anal. calcd.: N, 14.39; C, 37.01; H, 1.73
Found: N, 14.47; C, 36.93; H, 1.68

EXAMPLE 3

2-(3-Pyridyl)-4(5)-bromo-5(4)-trifluoromethylimidazole

To a suspension of 2 - (3 - pyridyl) - 4 - trifluoromethylimidazole (2.1 g., 0.01 mole) in chloroform (100 ml.) is added dropwise with stirring at room temperature bromine (1.6 g., 0.01 mole) in chloroform (5 ml.). The resulting solution is stirred for four hours at room temperature and concentrated at 20 mm. pressure over steam to a solid. Water (25 ml.) is added to the residue. The resulting solution is neutralized with saturated aqueous sodium bicarbonate solution to yield a solid. After filtration and recrystallization from acetonitrile, 1.15 g. of 2 - (3 - pyridyl) - 4(5) - bromo-5(4) - trifluoromethylimidazole is obtained, m.p. 227—228°C.

Anal. calcd.: N, 14.39; C, 37.01; H, 1.73
Found: N, 14.35; C, 37.13; H, 1.61

EXAMPLE 4

2 - (3 - Pyridyl) - 4,5 - dibromoimidazole

To a suspension of 2 - (3 - pyridyl) - imidazole (1.5 g., 0.01 mole) in chloroform (150 ml.) is added dropwise with stirring at room temperature bromine (3.2 g., 0.02 mole) in chloroform (5 ml.). Stirring is continued for 2 hours at room temperature. The chloroform is removed by decantation and the residual material is triturated with water (25 ml.) containing sodium bisulfite (1 g.). The resulting solid is removed by filtration and recrystallized from acetonitrile to yield 0.7 g. of 2 - (3-pyridyl) - 4,5 - dibromoimidazole, m.p. 226—227°C.

Anal. calcd.: N, 13.87; C, 31.72; H, 1.66
Found: N, 13.77; C, 31.73; H, 1.63

EXAMPLE 5

2 - (2 - Methyl - 3 - pyridyl) - 4(5) - bromo-5(4) - trifluoromethylimidazole

The procedure in Example 2 is repeated using 2 - (2 - methyl - 3 - pyridyl) - 4 - trifluoromethylimidazole (2.27 g., 0.01 moles) in place of 2 - (4 - pyridyl) - 4 - trifluoromethylimidazole to obtain 2 - (2 - methyl - 3-pyridyl) - 4(5) - bromo - 5(4) - trifluoromethylimidazole.

EXAMPLE 6

Hard Gelatin Capsules

	Gm.
2 - (3 - pyridyl) - 4,5 - dichloro imidazole	200
Cornstarch	150
Magnesium stearate, powder	50
Talc	50

The finely powdered ingredients are mixed thoroughly and then encapsulated in 1000 two-piece hard gelatin capsules each containing 200 mgs. of 2 - (3 - pyridyl) - 4,5 - dichloroimidazole.

EXAMPLE 7

Tablets

1000 Tablets each containing 100 mgs. of 2 - (4 - pyridyl) - 4(5) - bromo - 5(4) - trifluoromethylimidazole are prepared from the following ingredients:

	Gm.
2 - (4 - pyridyl) - 4(5) - bromo - 5(4)-trifluoromethylimidazole	100
Lactose	50
Starch	50
Calcium stearate	10
Talc	10

The finely powdered ingredients are mixed thoroughly and then tableted by a slugging procedure.

EXAMPLE 8

Hard Gelatin Capsules

Five thousand two-piece hard gelatin capsules, each containing 400 mg. of 2 - (3-pyridyl) - 4(5) - bromo - 5(4) - trifluoromethylimidazole are prepared from the following ingredients:

	Gm.
2 - (3 - pyridyl) - 4(5) - bromo-5(4) - trifluoromethylimidazole	2000
Lactose	3000
Magnesium stearate	1000
Talc	1000

The finely powdered ingredients are mixed thoroughly and then encapsulated by conventional techniques.

EXAMPLE 9

Anti-Hypertensive Activity

The procedure for evaluating the anti-hypertensive activity of the active agents comprises administering the compound either orally or intraperitoneally in spontaneously hypertensive rats of the Wistar-Okamoto strain. Arterial pressure is recorded continuously in these animals through an indwelling aortic catheter introduced through the caudal artery. The animals are allowed free movement in the metabolism cages during the measurements.

When the compounds of the present invention are tested intraperitoneally, distinct anti-hypertensive activity is noted. The compounds also show anti-hypertensive activity when tested orally.

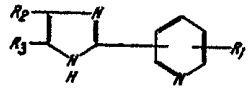
EXAMPLE 10

Xanthine Oxidase Inhibition

For testing purposes, xanthine oxidase obtained from milk may be used to demonstrate the ability of the imidazoles to inhibit the enzyme. The general procedure is to use a 5—10 unit suspension of the enzyme per milliliter of 60% saturated ammonium sulfate; 1 unit of such a suspension converts 1 μ mole of xanthine to uric acid per minute. Generally, for a 1-day assay, about 0.05 ml. of enzyme is diluted with about 3 ml. of buffer. As the buffer, tris buffer (tromethamine) (0.05 mole) pH 7.4 may be used. The inhibitor to be tested is dissolved in buffer or a suitable solvent, such as dimethylsulfoxide; the same solvent is used to dilute the solution. The buffer, hypoxanthine and solvent are placed in a cell, and the resulting solution is shaken to absorb air. The diluted enzyme solution is then added, and the rate of increase in absorbance at 290 mμ is noted with a recording spectrophotometer. Generally, sufficient enzyme is used to give about 0.1 absorbance units change per minute, and sufficient inhibitor is used to give 30—70% inhibition. The μM concentration of inhibitor necessary for 50% inhibition ($V_0/V_1=2$) is determined by plotting V_0/V_1 against I, where V_0=velocity without inhibitor, V_1=velocity with inhibitor, and I=inhibitor concentration. The activity of the tested compound is expressed in terms of percent inhibition. When the compounds of the present invention are tested in the above manner for xanthine oxidase inhibition, distinct activity is noted.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R_1 is a hydrogen atom or a C_{1-3} alkyl radical, R_2 is a halogen atom and R_3 is a halogen atom or a trifluoromethyl radical.

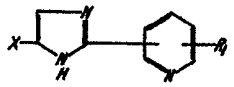
2. A pharmaceutically acceptable salt of a compound as claimed in Claim 1.

3. A compound as claimed in Claim 1 or 2 in which R_1 is hydrogen and R_2 and R_3 are chlorine.

4. A compound as claimed in Claim 1 or 2 in which R_1 is hydrogen, R_2 is bromine and R_3 is $-CF_3$.

5. A compound as claimed in Claim 1 in which R_1 is hydrogen and R_2 and R_3 are bromine.

6. A method of making a compound as claimed in Claim 1 or 2 that comprises reacting a compound of the formula:



wherein R_1 is as defined in Claim 1 and X is a hydrogen atom or a trifluoromethyl radical or a pharmaceutically acceptable salt thereof with a halogenating agent in an inert solvent.

7. A method as claimed in Claim 6 in which the reaction is carried out at a temperature of from −100°C. to 200°C.

8. A method as claimed in Claim 7 in which the reaction is carried out at a temperature of from −15°C. to 150°C.

9. A method as claimed in Claim 8 in which the reaction is carried out at a temperature of from 0°C. to 125°C.

10. A method as claimed in any one of Claims 6—9 in which the halogenating agent is free halogen.

11. A method as claimed in any one of Claims 6—9 in which the halogenating agent is N-chlorosuccinimide.

12. A method as claimed in any one of Claims 6—11 as applied to the preparation of a compound as claimed in Claim 3.

13. A method as claimed in any one of Claims 6—10 as applied to the preparation of a compound as claimed in Claim 4.

14. A method as claimed in any one of Claims 6—10 as applied to the preparation of a compound as claimed in Claim 5.

15. A method as claimed in Claim 6 substantially as hereinbefore described in any one of Examples 1—5.

16. A compound as claimed in Claim 1 when prepared by a method as claimed in any one of Claims 6—15.

17. A method of inhibiting xanthine oxidase or lowering blood pressure in a non-human animal that comprises administering to the animal a therapeutically effective amount of a compound as claimed in any one of Claims 1—5 and 16.

18. A method as claimed in Claim 17 in which the amount of the compound

administered is from 0.005 to 300 mg./kg of body weight of the animal.

19. A method as claimed in Claim 18 in which the amount of the compound administered is from 0.05 to 100 mg./kg. of body weight of the animal.

20. A method as claimed in Claim 19 in which the amount of the compound administered is from 0.1 to 25 mg./kg. of body weight of the animal.

21. A pharmaceutical composition comprising an inert pharmaceutically acceptable diluent and a compound as claimed in any one of Claims 1—5 and 16.

22. A composition as claimed in Claim 21 containing from 1 mg. to 2,000 mgs. of the said compound per unit dose.

23. A composition as claimed in Claim 22 containing from 5 mgs. to 1,000 mgs. of the said compound per unit dose.

24. A composition as claimed in Claim 23 containing from 10 mgs. to 500 mgs. of the said compound per unit dose.

25. A composition as claimed in any one of Claims 21—24 in the form of a tablet, pill, capsule, powder, granule, sterile parenteral solution or suspension or orally administrable solution or suspension.

26. A composition as claimed in Claim 21. substantially as hereinbefore described in any one of Examples 6 to 8.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD.

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